2026 Summer Research Fellowship Program Application

Project Description (1-2 pages)

Title: Impact of Catechol-O-Methyltransferase (COMT) Genetic Polymorphisms on the Effectiveness of COMT Inhibitors

Principal Investigator: Xinwen Wang, Ph.D.

Assistant Professor, Department of Pharmaceutical Sciences

College of Pharmacy, NEOMED

E-mail: xwang2@neomed.edu

Abstract

Parkinson's Disease (PD), the second most common neurodegenerative disorder worldwide, affects approximately 1% of individuals over age 60(Rizek, Kumar, & Jog, 2016). catechol-O-methyltransferase (COMT) inhibitors are widely used as adjunctive therapy to enhance levodopa therapy by blocking COMT-mediated levodopa metabolism. However, patient responses to COMT inhibitors vary, a significant portion of the patients do not benefit from the combined therapy(Gray, et al., 2022). There is a critical clinical need to identify the factors may influence how effectively these drugs suppress COMT activity and thereby enhance levodopa activation. Single nucleotide polymorphisms (SNPs) within the COMT gene, particularly rs4633, rs4818, and rs4680, have been associated with poor response to levodopa therapy in PD patients (Lin, Fan, Lin, Chang, & Wu, 2018). Despite their high population frequencies, the molecular consequences of these variants and haplotypes on COMT inhibitor responsiveness remain poorly defined. This project aims to characterize how rs4633, rs4818, and rs4680 and their haplotypes influence COMT expression and activity, and consequently, the magnitude of COMT inhibitor–mediated enhancement of levodopa activation. Findings will provide crucial mechanistic insight to inform precision therapy in PD.

Goals and Objectives

The overarching goal of this proposal is to establish a scientific foundation for optimizing the use of COMT inhibitor as an adjunctive therapy with levodopa for PD patients.

Our central hypothesis: COMT variants, rs4633, rs4818, and rs4680, may alter COMT expression or enzymatic function, which in turn may modulate the pharmacodynamic effectiveness of COMT inhibitors.

Specific Aim: Characterize how COMT single variants, rs4633, rs4818, and rs4680, and haplotypes alter basal COMT activity and modulate the inhibitory effectiveness of COMT inhibitors on levodopa metabolism.

Significance

This project addresses a critical but underexplored area at the intersection of pharmacogenomics and neurotherapeutics: the impact of COMT genetic polymorphisms on the pharmacodynamic effectiveness of COMT inhibitors used in Parkinson's disease (PD). COMT inhibitors are essential adjunctive therapies designed to enhance levodopa activation by blocking COMT-mediated metabolism(Rizek, et al., 2016). However, substantial interindividual variability in treatment response remains unexplained, posing major challenges for optimizing PD pharmacotherapy(Gray, et al., 2022). While genetic variants in COMT have been associated with poor responses to levodopa treatment(Lin, et al., 2018), their consequences for the inhibitory effectiveness of COMT inhibitors, and ultimately for levodopa metabolism, remain poorly understood. This gap limits our ability to develop precision treatment strategies for PD patients.

The project's focus on how COMT single variants and haplotypes influence COMT susceptibility to COMT inhibitor provides new mechanistic insight into how inherited genetic differences shape response to PD treatments. This is essential for optimizing PD treatment plans, especially given the prevalence of COMT polymorphisms and the high clinical reliance on COMT inhibitors in elderly patients with complex medication regimens. A clearer understanding of variant-driven changes in COMT activity will help explain therapeutic variability, reduce treatment failures, and minimize unnecessary dose escalation or polypharmacy.

By integrating pharmacogenomics, enzymology, and quantitative proteomics, this work addresses urgent needs in refining existing PD therapies and guiding the development of genotype-informed treatment strategies. It identifies key biological barriers to effective COMT inhibitor use and introduces a framework for predicting drug response based on genetic background. The findings will shape future pharmacogenomic research in PD, offering a scientific foundation for improving the efficacy and safety of levodopa-based treatment and contributing impactful knowledge to both neurodegenerative disease research and precision pharmacotherapy.

Research Methods

Generation of COMT Variant-Expressing Cell Lines

We will generate isogenic Flp-In-293 cell lines stably expressing wild-type COMT, each COMT single variant (rs4633, rs4818, rs4680), and their five major haplotypes. DNA extracted from each cell line will be sequence-verified to confirm correct variant or haplotype incorporation. Microsomal fractions will be prepared for COMT protein quantification and activity assays. COMT protein levels will be determined using targeted proteomics or capillary Western blotting (JESS).

Evaluation of COMT Inhibitor Effectiveness Across Variants

To determine which COMT variants/haplotypes alter the pharmacodynamic effectiveness of COMT inhibitors, each microsomal preparation will be incubated with a fixed concentration range of a representative COMT inhibitor, entacapone. Inhibition curves will be generated by measuring residual methylated levodopa metabolites via mass spectrometry. COMT inhibitor effectiveness will be evaluated using inhibitor dose–response assays to generate IC_{50} and Ki values, enabling comparison of how each variant or haplotype modifies COMT inhibition by entacapone.

Data Analysis and Expected Results

- Generate Michaelis–Menten and inhibitory kinetic models to evaluate differences in catalytic efficiency (V_{max}/K_m) and inhibitor sensitivity (IC_{50} or Ki).
- Use one-way ANOVA to compare COMT expression, basal activity, and inhibitor potency across SNPs and haplotypes.
- Correlate expression levels with inhibitory response to determine whether and how genetic variation influences inhibitor effectiveness.

We expect COMT variants and haplotypes to show measurable differences in COMT expression and basal enzymatic activity. Variants with higher intrinsic activity will likely require higher concentrations of COMT inhibitors to achieve comparable inhibition, reflected in elevated IC_{50} or Ki values. Conversely, lower-activity variants should be more easily inhibited. Haplotype effects are expected to be more pronounced than single SNP effects, identifying specific genetic combinations that reduce the effectiveness of COMT inhibitors in suppressing levodopa metabolism.

Student Fellow Training/Mentoring Plan (Limit of one half page)

Science Mentoring Plan

With regarding to the basic science training for the proposed project, the key areas I would like to help the student improve are listed as below:

a) Area: Pharmacogenomics in Parkinson's Disease

- We have Journal Club to share research trend/development and critically evaluate published articles in the field. In the Journal Club, the student will be participating in the discussion of current development in our fields. We will critically discuss the cons & pros of the research, and how the study may be designed differently to better answer the research questions.
- We have weekly lab meeting to discuss the research progress of the summer project and guide the students for trouble shooting.

b) Skills: Transformation, Transfection, Cell culture and LC-MS/MS sample preparation

- One-on-one mentoring will be offered to help student learn how to do transformation/transfection, culture transfected cells and extract intracellular and extracellular endogenous metabolites.

Presentation skills development

- The student will present the research updates weekly in our lab meeting and present articles in our Journal Club and DOM meeting.
- The student will also have opportunity to present the whole project in our department seminar after summer.
- The student will have opportunity to present at NEOMED research symposium.

Scientific Writing

a) Read publications on scientific Journal

- Reading well-written scientific articles is the key to learn and improve scientific writing. At the beginning, student will learn to search for references of interest using Google Scholar and PubMed, and perform literature review in relevant field. We will update the reading progress in Journal Club.

b) Practice and Revise

- Practice is necessary to improve writing skills. I find the writing-revision cycles between trainee and faculty is a very efficient and individualized way to polish writing skills. I will find opportunities for the student to improve writing skill through the personalized writing-revision cycles.

References:

Gray, R., Patel, S., Ives, N., Rick, C., Woolley, R., Muzerengi, S., Gray, A., Jenkinson, C., McIntosh, E., Wheatley, K., Williams, A., & Clarke, C. E. (2022). Long-term Effectiveness of Adjuvant Treatment With Catechol-O-Methyltransferase or Monoamine Oxidase B Inhibitors Compared With Dopamine Agonists Among Patients With Parkinson Disease Uncontrolled by Levodopa Therapy: The PD MED Randomized Clinical Trial. *JAMA Neurol, 79*, 131-140.

Lin, C. H., Fan, J. Y., Lin, H. I., Chang, C. W., & Wu, Y. R. (2018). Catechol-O-methyltransferase (COMT) genetic variants are associated with cognitive decline in patients with Parkinson's disease. *Parkinsonism Relat Disord, 50*, 48-53.

Rizek, P., Kumar, N., & Jog, M. S. (2016). An update on the diagnosis and treatment of Parkinson disease. *Cmaj, 188*, 1157-1165.